

## AMENDMENTS

### In the Claims:

Please amend the claims as follows:

A1  
7. (Amended) The method of claim 1, wherein the data accessed comprises data from the PSD-95 (Postsynaptic density protein of Mr 95kDa), Dlg (Drosophila Discs-Large protein) and ZO-1 (Zonula occludens protein 1) domain family.

A2  
16. (Amended) The method of claim 10, wherein the data accessed comprises data from the PSD-95 (Postsynaptic density protein of Mr 95kDa), Dlg (Drosophila Discs-Large protein) and ZO-1 (Zonula occludens protein 1) domain family.

## REMARKS

### **A. Status of the Claims**

Claims 1-34 were filed. A restriction requirement was then received. In response, Applicants elected to prosecute the Group I claims (i.e., claims 1-18) without traverse. The Office then canceled claims 19-34. Thus, claims 1-18 were pending at the time of the first Office Action.

Claims 7 and 16 have been amended. A marked-up copy of the amended claims is provided at Appendix A. A clean copy of the pending claims, after amendment, is attached for the Office's convenience at Appendix B.

### **B. The Claim Objections Are Overcome**

The Office objects to claims 2 and 11 as being improper dependent claims. The Office states, "The methods of 'executing using a machine' do not further limit the methods of claim 1 or 10, which include in the steps of the method accessing data." First Office Action, page 2. Applicants respectfully traverse.

Claims 1 and 10 do not require that any aspect of any step of either be performed or executed using a machine. By contrast, a machine must be used in claims 2 and 11 to execute the method of claims 1 and 10, respectively. Thus, claims 2 and 11 “further limit[] another claim or claims [i.e., claims 1 and 10, respectively] . . . .” 37 C.F.R. § 1.75(c). Applicants request that the objection be withdrawn.

Claims 7 and 16 have been amended to spell out the acronym PDZ. Accordingly, the objection to these two claims should be withdrawn.

**C. The 35 U.S.C. § 101 Rejections Are Overcome**

Claims 1, 2, 4-11, and 13-18 stand rejected under 35 U.S.C. § 101 as being directed to non-patentable subject matter. The Office cites various sections of the MPEP in support of its rejection, and notes that the claimed subject matter “may be claimed in combination with other functional descriptive multimedia material on computer-readable medium to provide the necessary functional and structural interrelationship to satisfy the requirements of 35 U.S.C. § 101.” Applicants respectfully traverse this rejection.

Claims 1, 2, 4-11, and 13-18 are patentable in light of *AT&T Corp. v. Excel Communications, Inc.*, 172 F.3d 1352, 1357-58 (Fed. Cir. 1999) (copy enclosed), which clarifies that processes involving algorithms need only apply the algorithm in a useful way to fall within § 101. In claim 1, the claimed algorithm is applied in identifying one or more positions within a multiple sequence alignment that have statistically significant conservation energy values. The identification of such positions “may be used, for example, to identify the active site (the functional surface), binding site, or allosteric site of a protein.” Specification, page 19, lines 10-11. Thus, the identified positions are useful, non-abstract results that facilitate the identification of these sites of a protein. As such, claims 1, 2, and 4-9 fall squarely within section 101.

Furthermore, other useful functions resulting from the original identification of the one or more positions, and the subsequent identification of the various sites of a protein, may include, for example, the identification of “a) positions in biological sequences that appear to be evolutionarily conserved, and b) positions in biological sequences that appear to interact with one another.” *Id.*, page 7, lines 6-9.

In claim 10, the claimed algorithm is applied in calculating a conservation energy value for each position in a multiple sequence alignment using the claimed algorithm. Such a conservation energy value or values is a useful, non-abstract results that may then be used in identifying one or more positions within a multiple sequence alignment that have statistically significant conservation energy values. The value of identifying such positions is explained above. Accordingly, claims 10-11 and 13-18 fall squarely within section 101.

For at least these reasons, Applicants respectfully submit that claims 1, 2, 4-11, and 13-18 are directed to patentable subject matter and request that the section 101 rejection be withdrawn.

**D. The 35 U.S.C. § 112 Rejections Are Overcome**

Claims 1 and 10 stand rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. With regard to claim 1, the Office asserts that “the steps taken in order to perform step (b) are not stated and it is unclear how this would be accomplished.” First Office Action, page 2.

Claim 1 is definite as filed considering Applicants’ ample description in the specification of how one can accomplish the identification of one or more positions in a multiple sequence alignment that have statistically significant conservation energy values using the claimed equation. Under the “DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS” heading of the

specification, Applicants detail an example of how to perform step (b) of claim 1. *See, e.g.*, page 19, line 21 – page 21, lines 20-28.

Considering this exemplary description of how to perform step (b) of claim 1 in light of the fact that “definiteness of claim language must be analyzed, *not in a vacuum*, but in light of: (A) the content of the particular application disclosure, (B) the teachings of the prior art, and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made” [MPEP § 2173.02, 2100-194 (emphasis added)], Applicants respectfully submit that claim 1 is definite.

Turning to the next indefiniteness rejection, the Office asserts that “[s]tep (b) and (c), [of claims 1 and 10] respectively, require calculation of statistical significance. However, significance values are not disclosed, leaving this essential step open to interpretation.” First Office Action, page 4. Applicants respectfully traverse this rejection for a number of reasons.

First, the phrase “statistically significant conservation energy values” is defined in the specification. Page 17, lines 14-19. Thus the meaning of this phrase is clear and, consequently, definite.

Furthermore, with respect to both indefiniteness rejections, it appears that the Office is equating claim breadth with indefiniteness. However, this is not the appropriate standard. MPEP § 2173.04 at 2100-195. For example, claim 1 need not recite every step that might be taken in performing step(b) for the same reason that a claim step directed to “breathing” need not recite “opening the mouth, expanding the lungs, drawing air past the lips, and exhaling.” Such is the stuff of specifications, not claims.

For at least these reasons, the rejected claims are definite, and the indefiniteness rejections should be withdrawn.

**E. The 35 U.S.C. § 103 Rejections Are Overcome**

Claims 1, 2, 4-6, 10, 11, and 13-15 stand rejected as being unpatentable over Ortiz et al., and further in view of LiCata et al. Applicants respectfully traverse this rejection.

**1. Claims 1, 2 and 4-6**

Claims 1, 2 and 4-6 require:

“(b) identifying one or more positions within the MSA that have statistically significant conservation energy values using the following equation:

$$\Delta G_i^{stat} = kT^* \sqrt{\sum_x \left( \ln \frac{P_i^x}{P_{MSA}^x} \right)^2}$$

wherein:

i is a position in the MSA;

$\Delta G_i^{stat}$  is the conservation energy value for position i;

$P_i^x$  is the probability of monomer x at position i;

$P_{MSA}^x$  is the probability of monomer x in the MSA; and

kT\* is an energy unit, where k is Boltzmann’s constant.”

The Office asserts that LiCata et al.’s alleged teaching of “a method for measuring the interaction between mutation site [sic] by measuring free energies that are associated with some function of the protein (page 3134)[,]” meets this limitation. First Office Action, page 5. However, the asserted disclosure of LiCata et al. – as well as the entirety of the cited references – lacks an explicit or necessarily inherent teaching or suggestion of the equation required by step (b) of claim 1.

Moreover, there is no motivation for the asserted combination of Ortiz et al. and LiCata et al. The fundamental premise of Ortiz et al. is that protein structures may be predicted based on the principle that evolutionary covariance predicts *close proximity* of positions. See page 317. By contrast, LiCata rejects this principle with their recognition of the existence of systematic

non-random energetic couplings in proteins that result from *non-contacting* residues. See, e.g., the title “Long-Range, Small Magnitude Nonadditivity of Mutational Effects in Proteins.” Considering the fundamental clash between the relative premises underlying these two works, no motivation exists for the asserted combination.

For at least these reasons, the Office has failed to make out a *prima facie* case of obviousness. Accordingly, the obviousness rejection of these claims should be withdrawn.

**2. Claims 10, 11, and 13-15**

Claims 10, 11, and 13-15 require:

- “(b) calculating a conservation energy value for each position in the MSA using the following equation:

$$\Delta G_i^{stat} = kT^* \sqrt{\sum_x \left( \ln \frac{P_i^x}{P_{MSA}^x} \right)^2}$$

wherein:

i is a position in the MSA;

$\Delta G_i^{stat}$  is the conservation energy value for position i;

$P_i^x$  is the probability of monomer x at position i;

$P_{MSA}^x$  is the probability of monomer x in the MSA; and

kT\* is an energy unit, where k is Boltzmann’s constant.”

The Office asserts that the same passage from LiCata et al. cited above meets this limitation. However, the asserted disclosure of LiCata et al. – as well as the entirety of the cited references – lacks an explicit or necessarily inherent teaching or suggestion of the equation required by step (b) of claim 10. Moreover, for at least the reasons explained above, there is no motivation for the asserted combination of Ortiz et al. and LiCata et al. Accordingly, the Office has failed to make out a *prima facie* case of obviousness, and the obviousness rejection of these claims should be withdrawn.

**APPENDIX A: MARKED-UP COPY OF AMENDED CLAIMS OF**  
**U.S. SERIAL NO. 09/684,066**

7. (Amended) The method of claim 1, wherein the data accessed comprises data from the [PDZ] PSD-95 (Postsynaptic density protein of Mr 95kDa), Dlg (Drosophila Discs-Large protein) and ZO-1 (Zonula occludens protein 1) domain family.
16. (Amended) The method of claim 10, wherein the data accessed comprises data from the [PDZ] PSD-95 (Postsynaptic density protein of Mr 95kDa), Dlg (Drosophila Discs-Large protein) and ZO-1 (Zonula occludens protein 1) domain family.